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CHRISTENSEN, O'CONNOR, JOHNSON, KINDNESS, PLLC
1420 FIFTH AVENUE
SUITE 2800
SEATTLE, WA 98101-2347

EXAMINER
LACOURCIERE, KAREN A

ART UNIT	PAPER NUMBER
1635	10

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/622,719	Applicant(s) LOEWENHEIM, HUBERT
	Examiner Karen Lacourciere	Art Unit 1635

-- The MAILING DATE of this communication appears on the cover sheet with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 28-61 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 28-61 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Information Disclosure Statement

Applicant should note, only the abstract of WO 97/04762 (reference AG on PTO form 1449, filed January 7, 2002) was considered, as only the abstract is in English and no translation was provided. References BE, BF, BG, BH and BI on PTO form 1449, filed January 7, 2002, were not considered because the citations were not proper, for example, the publication date, names of authors and publication location were not provided on PTO form 1449 as required under 37 CFR §1.98.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

The foreign priority document is in a foreign language and no translation was provided, therefore, the application has only been given priority to the filing date of the instant Application.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 28-61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 28-61 are indefinite because of the absence of an article in the preamble of the claim, rendering the scope of the preamble indefinite. The claims appear to follow

the European style, whereas in U.S. practice independent claims normally contain an article in the preamble.

Claim 30 is indefinite because there are no methods steps that arrive at the outcome set forth in the preamble of the claim. The claim is set forth as a method of preparing a pharmaceutical composition, however, the only active method step in the claim is "administering an active ingredient able to inhibit or eliminate the action of a cell cycle inhibitor present in the inner ear". It is unclear how this administration step relates to preparation of a pharmaceutical composition or medicament. For example, are the remaining steps missing from the claim? It is unclear what method is being claimed.

Claim 49, and claims dependent on claim 49, are indefinite because claim 49 is grammatically incorrect in the recitation "characterized in the it", making the claim unclear.

Claim 49 and claims dependent on claim 49 are indefinite because the phrase "the sensory cells of the inner ear" lacks antecedent basis.

Claim 49, and claims dependent on claim 49, are indefinite due to the recitation "in a position". It is unclear what characteristic "in a position" imparts to the claimed active ingredient, for example, does this phrase indicate that the active ingredient is only being claimed when it is physically in the inner ear, or does "in a position" indicate some other physical characteristic of the claimed active ingredient? It is unclear what limitation "in a position" is providing to the claimed active ingredient.

Claim 55 is indefinite because it is unclear if the phrase "in an active quantity" is referring to the active ingredient or the cell cycle inhibitor. Claim 56 is indefinite for the same reasons due to dependence on claim 55.

Claims 28, 31-48, 57 and 58 are directed to a process for the treatment of diseases or disorders of the inner ear but, since the claims do not set forth any steps involved in the process, it is unclear what process applicant is intending to encompass. The process is set forth by characterizing the outcome of the process, but does not actually recite any active, positive steps involved in the claimed process. A claim is indefinite where it merely recites a process without any active, positive steps delimiting how this process is actually practiced.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 29 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance

presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Claim 29 is drawn broadly to methods of treating generally any disease or disorder of the inner ear linked with damage or destruction of the sensory cells by administering generally any active ingredient able to inhibit or eliminate the action of generally any cell cycle inhibitor in the inner ear. Claim 29 would encompass treatment for a broad range of diseases and conditions using a broad range of compounds, including antisense and gene therapy method of treatment and would include methods wherein these compounds are administered directly to the ear (local administration) or systemically delivered compounds.

The specification provides examples wherein a $p27^{Kip1}$ knockout mouse is made and cells within the corti-organ of the mouse undergo cell division and these mice have more hair cells than normal mice. This example does not provide any demonstration of a treatment for any disease or disorder of the inner ear. There are no examples wherein any inhibitor of a cell cycle inhibitor is administered to a subject. There are no examples wherein any other cell cycle inhibitor (besides $p27^{Kip1}$) activity is knocked out or even reduced and sensory cell growth is affected. There are no examples wherein any disease or disorder of the inner ear is treated by inhibition of a cell cycle inhibitor. The specification does not provide any guidance on what specific diseases or disorders can be treated by inhibiting a cell cycle inhibitor, or what specific cell cycle inhibitor to target for inhibition to provide a treatment effect for a particular disorder or disease. There are no examples wherein antisense a gene therapy vector is delivered in vivo (whole

organism) nor wherein antisense or gene therapy methods are used to provide a treatment effect for any disease or disorder of the inner ear.

After the date the instant invention was made, the inventor of the instant application states, "A causal therapeutic option for sensorineural hearing loss is not yet available....A specific therapeutic modality directly applicable to the inner ear has yet to be developed." and "At present the only available therapeutic option is symptomatic in the form of hearing aids." (Pfister and Löwenheim, 2002, p53, center column).

The morphological development of the inner ear involves a complex series or developmental events (See for example, Chen et al.) and at the time the instant invention was made "the mechanisms that link developmental events to the cell cycle machinery that controls cell proliferation remain poorly understood" (Chen et al., p 1581, introduction, first column). Although cyclin-dependent kinase inhibitors were known to be involved in developmental events in the inner ear, "In spite of the advances in our knowledge of the regulation of CDK activity, little is known about how regulation of CKIs is integrated into specific developmental programs to coordinate cell proliferation with morphogenesis." (Chen et al. p 1582, first column). To provide a treatment effect for a disease or disorder of the inner ear, as claimed, it would require not only hair cell proliferation, but additionally differentiation, maturation, functional recovery and maintenance of the sensory cells. Although the specification demonstrates a role for one particular cell cycle kinase inhibitor in sensory cell development, the signaling pathways had not been elucidated to achieve control of the development of these cells in a specific manner and it was unclear whether the release of cells from inhibition of

proliferation would initiate the further events required to complete the hair cell regeneration process (see for example, Löwenheim et al., PNAS, 96, 1999, page 4088, last paragraph), as would be required to achieve a treatment effect for a disease or disorder of the inner ear. The specification has not provided any guidance by which one skilled in the art would know how to administer inhibitors for cell cycle inhibitors to control this process, in order to provide a treatment effect. Further, the preferred target for inhibition in the specification, $p27^{Kip1}$, appears to have roles not only in development, but also in cell maintenance (see for example, Chen et al.). The specification has not provided any information on how to specifically inhibit $p27^{Kip1}$ for regeneration, without affecting its role in cell maintenance, such that the outcome of administration of an inhibitor would be a treatment for a disease or disorder. Given the complexity of the pathways of sensory cell development, and the lack of available information on the timing and role of cell cycle inhibitors in these pathways, the skilled artisan would not be able to predictably control the development of these cells by administering inhibitors of cell cycle inhibitors, such that a treatment effect for a disease or disorder of the inner ear would be achieved, with out undue trial and error experimentation.

In addition to the problems specific to the treatment of inner ear disorders, the claims would encompass antisense and gene therapy methods of treatment. At the time the instant invention was made, the therapeutic use of antisense oligonucleotides was a highly unpredictable art due to obstacles that continue to hinder the therapeutic application of antisense *in vivo* (whole organism) (see for example Agrawal et al. (Molecular Medicine Today, Vol 6, p 72-81, February 2000), Branch (TIBS 23, Feb

1998, p45-50), Green et al. (J. Am Coll. Surg., Vol 191, No. 1, July 2000, p 93-105), Jen et al. (Stem Cells 2000, Vol. 18, p 307-319)). Such obstacles include, for example, problems with delivery, target accessibility and the potential for unpredictable nonantisense effects. Jen et al. state (see page 313, second column, second paragraph) "One of the major limitations for the therapeutic use of AS-ODNs and ribozymes is the problem of delivery....Presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable". Jen et al. outlines many of the factors limiting the application of antisense for therapeutic purposes and concludes (see p 315, second column), "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive."

Green et al. state, "It is clear that the evolution of antisense technology from a laboratory research tool into a mechanism for designing active and effective drugs is far from complete. Although there is little doubt that systemically administered antisense ODNs can inhibit the expression of specific genes in patients, the effectiveness of such therapy in modifying the course of a particular illness has not yet been established....Clearly, additional work must be done to unravel the complex problems associated with drug delivery, mRNA targeting and aptameric, nonantisense effects."

The specification has provided no guidance on how to administer antisense to a subject, to specifically target cells of the inner ear and treat a disease of condition of the inner ear using antisense, gene therapy or any other nucleic acid based therapy. The field of antisense, to date, does not provide guidelines by which antisense can be

routinely delivered to generally any cell type *in vivo* (whole organism) at a concentration effective to result in a predictable therapeutic effect, including cells of the inner ear. The specification does not provide specific guidance by which one skilled in the art would expect to be able to deliver nucleic acid based therapeutics, including antisense, to a target cell or tissue *in vivo* (whole organism) at a concentration effective to treat the broad range of inner ear diseases and disorders encompassed by the claims.

In order to practice the invention as claimed, the skilled artisan would need to under undue trial and error experimentation to determine how to control sensory cell development by administering inhibitors of cell cycle inhibitors, for example, which inhibitors to target for particular diseases and disorders, how to specifically target a particular cell cycle inhibitor, how long to administer a particular inhibitor, how to specifically deliver nucleic acid based inhibitors, and when to turn off and on particular cell cycle inhibitors to achieve a particular morphology, for example, in order to provide a treatment effect. Therefore, due to the breadth of the claims, the nature of the invention, the unpredictability recognized in the art, the lack of specific guidance and working examples in the specification and the quantity of experimentation required for the skilled artisan to practice the claimed invention, one skilled in the art would not be enabled to practice the claimed methods of treatment.

Claim 30 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one

skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 30 is directed to a method of preparing a pharmaceutical composition or medicament, wherein an active ingredient able to inhibit or eliminate the action of a cell cycle inhibitor present in the inner ear is administered.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The scope of the claim is broad, drawn to a method of producing generally any type of pharmaceutical composition or medicament for any disease or disorder of the sensory cells of the inner ear, wherein the only step disclosed is administering an active ingredient.

There is no guidance provided, in the specification or claims, as to what the active ingredient is administered to, what active ingredient is useful in the claimed method, what other steps are required to prepare the composition or medicament, and what types of pharmaceuticals or medicaments can be prepared using the claimed methods. The specification does not provide any working examples of the claimed method. The prior art does not provide guidance for the preparation of a pharmaceutical or medicament by the claimed method, therefore, the skilled artisan

would need to determine, de novo, how to practice the claimed method and, given that the specification is virtually silent with regard to how to practice the claimed method, this would need to be done by undue, trial and error experimentation.

Claims 28-61 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claims 29-30, 49-56 and 59-61 are drawn to active ingredients that inhibit the activity of a cell cycle inhibitor present in the inner ear, and methods that require these active ingredients. These active ingredients claimed, and methods claimed that require these active ingredients, encompass a very broad genus of compounds with highly variant structures. For example, the genus of active ingredients would encompass many types of inhibitors, including proteins, peptides, nucleic acids encoding proteins, inhibitory nucleic acids, small molecule inhibitors, and antibodies, and would encompass direct or indirect inhibitors of cell cycle inhibitors, each of which would have a different structure. Further, the genus of active ingredients would encompass inhibitors of a very broad genus of cell cycle inhibitors and cyclin dependent cell cycle inhibitors; inhibitors of various cell cycle inhibitors would vary widely in structure.

The specification has not provided the structure of any active ingredient encompassed by the claims. For example, although the specification suggests the

preferred embodiment of the claimed active ingredients would be inhibitors of $p27^{kip1}$, the specification has not provided any structure for inhibitors of $p27^{kip1}$, for example, there is no sequence for an antisense inhibitor, no mRNA sequence by which an antisense sequence could be determined, no amino acid sequence or structural information for a peptide inhibitor of $p27^{kip1}$, and not structural information has been provided for a small molecule inhibitor of $p27^{kip1}$. Additionally, the specification has not provided any information about what other cell cycle inhibitors would be inhibited to provide sensory cell regeneration, or the structure of active ingredients inhibiting these cell cycle inhibitors. The genus of active ingredients claimed is so broad that it may encompass compounds known in the prior art, generally any inhibitor of a cell cycle inhibitor, however, the specification has not provided sufficient description such that the skill artisan would recognize which prior art compounds have the desired activity, nor does the prior art provide a written description for the very broad genus claimed.

The specification has not provided the detailed chemical structure or common structural characteristics of these active ingredients, such that the skilled artisan would recognize that the inventor was in possession of the broad genus of active ingredients claimed, or required to practice the claimed methods, at the time the instant invention was made.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 28, 31-48, 57 and 58 are rejected under 35 U.S.C. 101 because the claimed recitation of a process, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claims 49-53, 59 and 60 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claims 49-53, 59 and 60 would encompass inhibitors of cell cycle inhibitors as they would exist in nature and, therefore, would encompass non-statutory subject matter. Stating that the active ingredients are isolated would obviate this rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 49-56, 59, 60, and 61 are rejected under 35 U.S.C. 102(b) as being anticipated by Hauser et al. (Cell Growth and Differentiation, Vol. 8, Feb 1997, p 203-211).

Hauser et al. disclose cell cycle inhibitors. Hauser et al. disclose protein inhibitors of cell cycle inhibitors; for example, Hauser et al. disclose antibodies that bind to $p27^{kip1}$. Hauser et al. disclose nucleic acids inhibitors of cell cycle inhibitors, for

example, antisense targeted to $p27^{kip1}$ administered to cells in liposomes. Hauser et al. do not disclose that these inhibitors have sensory cell regeneration properties, however, these inhibitors have all of the characteristics of the claimed active ingredients and are active against $p27^{kip1}$, the preferred embodiment of the instant specification and, therefore, would inherently have the activity claimed.

Therefore, Hauser et al. anticipates claims 49-56, 59, 60, and 61.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Lacourciere whose telephone number is (703) 308-7523. The examiner can normally be reached on Monday-Friday 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-1935 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Karen A. Lacourciere
PATENT EXAMINER

Karen A. Lacourciere
September 9, 2002